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Modelling the Mechanical Behaviour of a Pharmaceutical Tablet Using PDEs

Norhayati Ahmat, Hassan Ugail and Gabriela González Castro

Abstract Detailed design of pharmaceutical tablets is essential nowadays in order to produce robust tablets with tailor-made properties. Compressibility and compactibility are the main compaction properties involved in the design and development of solid dosage forms. The data obtained from measured forces and displacements of the punch are normally analysed using the Heckel model to assess the mechanical behaviour of pharmaceutical powders. In this paper, we present a technique for shape modelling of pharmaceutical tablets based on the PDE method. We extended the formulation of the PDE method to a higher dimensional space in order to generate a solid tablet and a cuboid mesh is created to represent the tablet's components. We also modelled the displacement components of a compressed PDE-based representation of a tablet by utilising the solution of the axisymmetric boundary value problem for a finite cylinder subject to a uniform axial load. The experimental data and the results obtained from the developed model are shown in Heckel plots and a good agreement is found between both.

1 Introduction

Tablets are the dominant dosage form for drug delivery in the pharmaceutical industry. This type of dosage form is convenient to use by patients, has long term storage stability and good tolerance to temperature changes. The quality of the tablet is determined by several parameters such as accurate mass, height and hardness. Thus, in order to produce quality tablets, it is important to understand the mechanical prop-

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erties of these tablets. Therefore, many studies have been carried out to investigate the compaction properties (compressibility and compactibility) of various types of excipients. Compressibility refers to the ability of the powder to deform under pressure [3] whereas compactibility is the ability of a powder bed to convert from small particles into a mechanically strong tablet [8].

The Heckel model is the most popular mathematical model for measuring the compressibility of pharmaceutical powders [3,9]. Thus, we employed this model to analyse the data of compressed powder over a PDE-based tablet. The linear Heckel equation is based on the relative density-pressure relationship,

$$\ln\left(\frac{1}{1-\rho_{\text{rel}}}\right) = PK + A, \tag{1}$$

where ρ_{rel} is the relative density, P is an axial pressure, and K and A are constants. The relative density is defined as the ratio of the density of a substance at pressure P to the true density of the material. The constant A is associated with particle rearrangements before deformation while the reciprocal of K is a measure of the particles yield pressure (P_y), which determines the hardness of powders [3]. Low values of P_y indicate harder tablets [9].

Recently, there has been a rapid expansion of computer uses in medical application especially in medical image processing [4] and drugs' design [5]. However, we have not found in the literature any work related to geometric modelling of pharmaceutical tablets based on the use of parametric surface representation. Therefore, the objective of this work is to model a solid cylindrical pharmaceutical tablet by utilising the PDE method [7] and to study the mechanical behaviour of the axially compressed PDE-based representation of a tablet.

2 Generating a Cylindrical Tablet Using the PDE Method

The PDE method generates parametric surfaces and it is based on the use of elliptic PDEs. The surface is defined by the two parameters u and v, in the region comprising $0 \leq u \leq 1$ and $0 \leq v \leq 2\pi$. The general form of an elliptic PDE over a two-dimensional domain is given by,

$$\left(\frac{\partial^2}{\partial u^2} + \alpha^2 \frac{\partial^2}{\partial v^2}\right)^r \underline{\chi}(u,v) = 0, \tag{2}$$

where $\underline{\chi}(u,v)$ is the function defining a surface in 3D space while α is a smoothing parameter [7] and r defines the order of the PDE. Equation (2) is transformed to the Biharmonic Equation by taking $r = 2$ and $\alpha = 1$. A smooth surface patch can be produced by solving the fourth order PDE analytically subject to a set of four periodic boundary conditions (BCs),

$$\underline{\chi}(0,v) = \underline{P}_0(v), \quad \underline{\chi}(1,v) = \underline{P}_1(v), \quad \underline{\chi}_u(0,v) = \underline{d}_0(v), \quad \underline{\chi}_u(1,v) = \underline{d}_1(v). \tag{3}$$

The overall shape of the PDE surface depends on the derivative conditions which are defined by the derivative vector along the boundary curves [7]. The analytic solution of the fourth order PDE can be written as,

$$\underline{\chi}(u,v) = \sum_{m=1}^{4} \underline{a}_{0m} u^{m-1} + \sum_{n=1}^{\infty} [\underline{A}_n(u)\cos(nv) + \underline{B}_n(u)\sin(nv)], \tag{4}$$

where

$$\underline{A}_n = (\underline{a}_{n1} + \underline{a}_{n3}u)e^{\alpha nu} + (\underline{a}_{n2} + \underline{a}_{n4}u)e^{-\alpha nu},\ \underline{B}_n = (\underline{b}_{n1} + \underline{b}_{n3}u)e^{\alpha nu} + (\underline{b}_{n2} + \underline{b}_{n4}u)e^{-\alpha nu}. \tag{5}$$

The first term in (4) traces the spine of the surface patch while $\sum_{n=1}^{\infty} [\underline{A}_n(u)\cos(nv) + \underline{B}_n(u)\sin(nv)]$ gives the radial position of a point $\underline{\chi}(u,v)$ away from the spine. The BCs are expressed as Fourier series in order to identify the constants in (4). The approximate solution to (4) can be found based on the sum of the first Fourier modes (typically $N = 6$) and a remainder function, $\underline{R}(u,v)$,

$$\underline{\chi}(u,v) = \sum_{m=1}^{4} \underline{a}_{0m} u^{m-1} + \sum_{n=1}^{N} [\underline{A}_n(u)\cos(nv) + \underline{B}_n(u)\sin(nv)] + \underline{R}(u,v), \tag{6}$$

where

$$\underline{R}(u,v) = (\underline{r}_1(v) + \underline{r}_3(v)u)e^{Nu(\alpha+1)} + (\underline{r}_2(v) + \underline{r}_4(v)u)e^{-Nu(\alpha+1)}, \tag{7}$$

Figure 1 presents an example of the PDE surface defined by 4 boundary curves.

Fig. 1 The shape of a surface generated by the PDE method; Boundary conditions in the form of curves (left). The resulting surface shape (right).

Many studies have been carried out to exploit the full potential of the PDE method in visual computing since the PDE surfaces offer many advantages over other type of surfaces. Most of all, this technique is capable of blending surfaces [1] and offers modelling tools to manipulate the shape of the PDE surface [7]. Moreover, smooth surfaces with high-order continuity requirements can be defined through PDEs since the formulation is well-conditioned and technically sound.

The geometric model representing a flat-faced cylindrical tablet used throughout this work has been designed using 10 generating curves to produce a surface composed of 3 patches. The adjacent surface patch is created by evaluating the BCs using the next set of curves. Each patch shares one boundary curve with either one or two different PDEs so that position continuity is guaranteed along the generated surface. As one can see in Fig. 2(a), the last curve of Patch 1 is used as the first curve of Patch 2. The output shape of the generated closed cylinder with radius 5 mm and height 6 mm can be seen in Fig. 2(b). Since the PDE method's formulation used in the early part of this section only generates the tablet's shell, then we extended (4) to a higher dimensional space by introducing a new parameter, w,

$$\underline{\chi}(u,v,w) = \sum_{m=1}^{4} \underline{a}_{0m} u^{m-1} + w \sum_{n=1}^{\infty} [\underline{A}_n(u)\cos(nv) + \underline{B}_n(u)\sin(nv)], \tag{8}$$

where $0 \leq w \leq 1$. This new parameter generates the interior points of the tablet, from the spine towards the point $\underline{\chi}(u,v)$ on the surface. A cuboid mesh is produced to represent the tablet's inner part as illustrated in Fig. 2(c). The number of nodes and cuboids used to generate the solid object depend on parameters u, v and w. For example, the number of cuboids in Fig. 2(c) is 12 000 when the parameters are defined as $u = w = [0, \frac{1}{20}, \frac{1}{10}, ..., 1]$ and $v = [\frac{\pi}{2}, \frac{11\pi}{20}, ..., 2\pi]$.

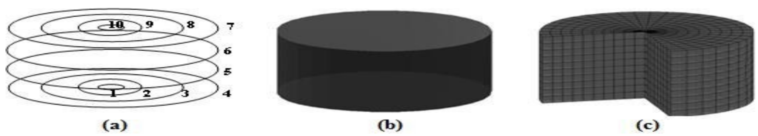

Fig. 2 Cylindrical tablet generated using the PDE method; Boundary curves (a), Resulting PDE surface (b), Solid cylindrical tablet with domain $0 \leq u,w \leq 1$ and $\frac{\pi}{2} \leq v \leq 2\pi$ (c).

3 Compression of a Cylindrical Tablet

Tablets composed of 300 mg of α-lactose monohydrate were prepared through the Single Ended Compression (SEC) process. The powder was poured into a cylindrical die of radius (c) 5mm with an initial height (h_0) of the powder bed equal to 6mm. The measured true density of this powder has been reported to be 1.3 mg/mm^3. The compression pressures applied on the powder bed were ranging from 0.05 to 70 MPa in order to obtain a tablet of 3mm in height. Since the radius of the die is fixed, only the axial displacement is involved in this process. The experimental data were analysed using the Heckel model and only data from pressure 10 MPa up to 50 MPa have been used because this range showed the best linearity which represents particle deformation.

In order to model the mechanical behaviour of an axially compressed cylindrical PDE-based tablet, a three-dimensional analytical solution for a uniformly loaded finite, homogeneous and isotropic cylinder has been adopted [2]. The solution is obtained by utilising the Biharmonic Love's stress function $\phi(r,z)$ with 8 terms,

$$\phi = \frac{a_6}{3}(16z^6 - 120z^4r^2 + 90z^2r^4 - 5r^6) + b_6(8z^6 - 16z^4r^2 - 21z^2r^4 + 3r^6) + b_3(z^3 + zr^2)$$
$$+ a_3(2z^3 - 3zr^2) + a_4(8z^4 - 24z^2r^2 + 3r^4) + b_4(2z^4 + z^2r^2 - r^4) + a_2(2z^2 - r^2) + b_2(z^2 + r^2), \tag{9}$$

where a_i and $b_i (i = 2,3,4,6)$ are determined from the BCs. For the axisymmetric problem, the stress and displacement components can be expressed in terms of $\phi(r,z)$ [6] as,

$$\sigma_z = (2-\gamma)\frac{\partial}{\partial z}\nabla^2\phi - \frac{\partial^3\phi}{\partial z^3}, \qquad \tau_{rz} = (1-\gamma)\frac{\partial}{\partial r}\nabla^2\phi - \frac{\partial^3\phi}{\partial r\partial z^2}, \tag{10}$$

$$\mu_r = -\frac{1+\gamma}{E}\frac{\partial^2\phi}{\partial z\partial r}, \qquad \omega_z = \frac{1+\gamma}{E}\left[2(1-\gamma)\nabla^2\phi - \frac{\partial^2\phi}{\partial z^2}\right], \tag{11}$$

where E is the Young modulus and γ is the Poisson's ratio.

The axial displacement of the compressed PDE-based tablet is obtained by substituting (9)-(11) into the following set of BCs,

$$\sigma_z\big|_{z=0} = 0,\;\; \sigma_z\big|_{z=h_0} = -P,\;\; \tau_{rz}\big|_{z=0,h_0} = 0,\;\; \omega_z\big|_{z=0} = 0,\;\; \mu_r\big|_{r=c} = 0,\;\; \frac{\partial\omega_z}{\partial r}\big|_{z=0} = 0. \tag{12}$$

Thus, the axial displacement component can be written as,

$$\omega_z = \omega_{z0} + \frac{100Pz^2(1+\gamma)}{Eh_0}\left[\frac{z^2\gamma}{r^2} - \frac{(1-\gamma)}{2} + \frac{\gamma^2}{\gamma-1}\left(1-\frac{c^2}{r^2}\right)\right], r > 0, \tag{13}$$

where z and r are any point in z and r directions respectively and ω_{z0} is an adjustment constant which is obtained from the difference between the initial axial displacement of the compressed pharmaceutical powder and the PDE-based tablet.

The change in the PDE-based tablet height due to axial pressure ranging from 10 MPa to 50 MPa are measured using (13) with E = 2.64 GPa, γ = 0.21 and $\omega_{z0} = -1.07$ mm, and the results are plotted as a Heckel graph. The Heckel plot of the compressed lactose powder and PDE-based tablet can be seen in Fig. 3. From the graph, it is found that the P_y of α-lactose is slightly higher than the one obtained from our model, where their values are 103.09 MPa and 93.46 MPa respectively. This is expected because the generated PDE-based tablet does not take the particle size and the degree of porosity into account.

The results shown in Fig. 3 prove that the solution of the Love's stress function can be utilised to measure the axial displacement of the compressed PDE-based tablet. However, the validity of the developed model is only verified at the lower pressure, where it indicates the deformation of the powder. Furthermore this model can only be applied to a cylindrical tablet defined by a set of BCs that depend on the chosen tabletting process, which in this case is the SEC process. Consequently, a more general model for characterising the stress distribution must be developed.

4 Conclusions

The work presented in this paper focuses on the application of the PDE method for designing a parametric representation of a cylindrical pharmaceutical tablet. Three smooth surface patches generated by a fourth order PDE have been blended together to construct a hollow cylindrical tablet. The solid PDE-based tablet is generated by extending the PDE method to a higher dimension by introducing an additional parameter, w into the analytic solution of the elliptic PDE. The axial displacement

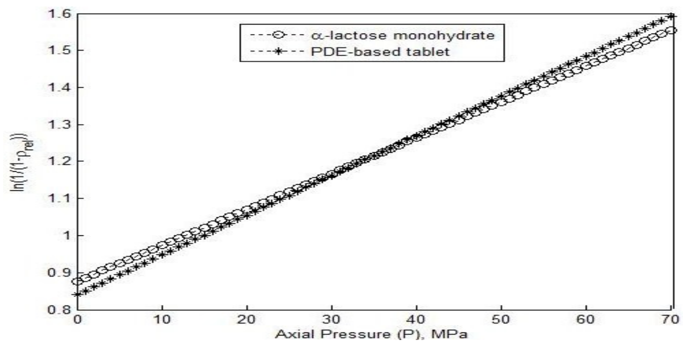

Fig. 3 Heckel plot of the simulated compression and experiment on lactose powder.

component of a compressed PDE-based tablet is measured by utilising one of the solutions of the Love's stress function found in the literature to model compaction of tablets. Heckel analysis is employed to analyse the results obtained from the developed model and is compared with the experimental results. It is found that the theoretical Heckel's parameter is quite similar to the experimental ones. However, the developed model seems to underestimate the initial volume of the particle bed. Additionally, the output of this model is sensitive to the change of the elastic properties such as the Young Modulus and the Poisson's ratio..

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